Point Mutations

Introduction

This lesson is about the mutations that impact transcription—micro mutations that are a point mutation, which can really lead to disastrous results. Chromosomal abnormalities at the chromosome-in-mitosis level (crossover events, aneuploidy) will be discussed in medical genetics. We're talking about what happens when the DNA has a single change of a nucleotide. That change gets transmitted to the mRNA, and the ultimate effect is what happens to the amino acid sequence as a result of that initial DNA change.

While there could be an error in the copying of genetic material from DNA to mRNA (transcription) and that would result in the following issues, that change is not propagated in the cell line. If a single transcription event suffers an error, the protein it makes will be bad. But mRNA is a low-fidelity product; mRNA polymerase has no proofreading. Since the mRNA is going to be degraded anyway, this often does not impact the organism long-term. The cell can just make another mRNA copy and wait for the bad one to expire. If the mutation is trapped in the genetic code because it's propagated into the DNA, however, the organism is going to feel it.

Changing just a single nucleotide has a variable presentation. A point mutation may be silent, missense, or nonsense.

Transitions and Transversions

A **point mutation** is the changing of one nucleotide to another. That is, a single letter gets changed. We call a point mutation a **transition** when there's a change to the same type of base (a purine to a purine or a pyrimidine to a pyrimidine). We call a point mutation a **transversion** when there's a change between types of base (a purine for pyrimidine or vice versa). In a point mutation **nothing is added or deleted**; a single nucleotide simply changes, thereby changing the codon.

Three Responses to Point Mutation

A **silent** mutation is one that isn't felt. The **phenotype stays the same**. Even though a nucleotide changed, which means the codon changed, the codon that mutation created shared the same amino acid as the original codon. That means **no change in amino acid** so **no change in function of protein**. We know that there are duplicates—there are more codons than there are amino acids. We know that the **third base** in the codon is **degenerate** and that an anticodon experiences a **wobble effect**. Effectively, that means that the **third base** in a codon, and only the third, could have a mutation that results in no effect at all. The only way it'd be detected is if the DNA were run and we knew what it was supposed to be. Again, this is the third position. If it happened to a first or second nucleotide position, there would be a definitive change in the amino acid. Silent mutations, by definition, have the identical primary, secondary, and tertiary protein structures—only the DNA changes.

A **missense** mutation is one that's felt, but not bad. The **phenotype changes**. The point mutation you incurred actually had an **amino acid switch**. This could be mild and asymptomatic, or it could be quite severe. **Sickle Cell Anemia** is a single amino acid switch from a **valine to glutamate at position 6**. That single amino acid change takes normal Hgb A (which doesn't sickle ever, doesn't cause anemia, doesn't block capillaries causing crippling joint pain and autosplenectomy) and makes Hbg S (which does). It's autosomal recessive, so you need both copies to have the switch, but it's prevalent enough, especially in African Americans, where it's not an uncommon disease. These patients die in their 40s, suffer vaso-occlusive crises (acute chest, pulmonary edema, stroke, priapism), and generally deal with crippling debilitating pain. This change in function is dramatic, but also illustrates how important every amino acid in the sequence is to maintaining function. Missense mutations often have the same length amino acid chain but with different amino acids, meaning that the primary structure is abnormal, making secondary, tertiary, and quaternary also abnormal.

A **nonsense** mutation is bad. The point mutation either **creates a premature stop** (the protein is useless) or it **eliminates a stop codon** so the ribosomes just keep going until they run out of strand. Both of these changes cause complete loss of function of the gene, which means that no protein can be made. On the test, they'll use this to assess if you know how proteins work. Almost certainly there will be a premature stop codon. It'll then be up to you to decide "how bad is it?" The closer to the 5' end, i.e., the closer to the beginning of the protein, the less normal protein gets made (and the worse it is). The closer to the 3' end aka the closer to the end of the protein, the more normal protein gets made before it encounters the error (the not-as-bad-it-is). But certainly, if a simple change of one amino acid can provoke sickle cell anemia, think what missing half of the protein would do! Nonsense mutations almost always have a different sized amino acid sequence—either much shorter (premature stop) or much longer (loss of stop) than the original sequence.

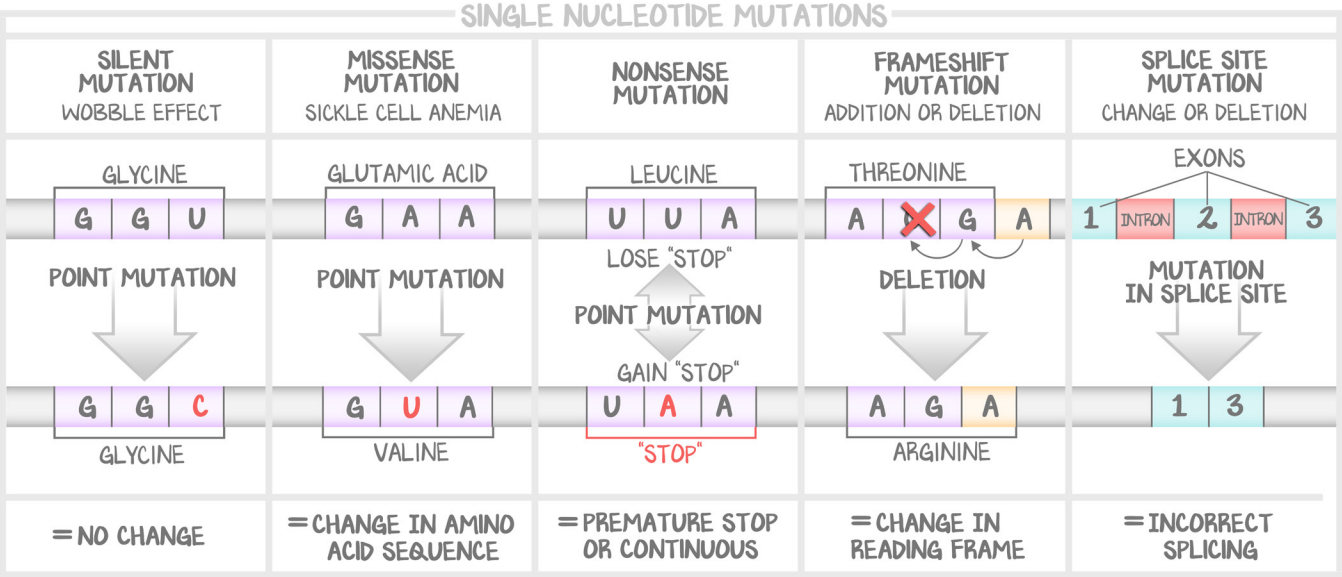

Figure 15.1: Single Nucleotide Mutation Consequences
All the different point mutations and their responses.

Other Single Nucleotide Mutations

Frameshift mutation requires a change in the number of nucleotides and is caused by an addition or deletion (most often caused by a **deletion**). It's still a point mutation because only **one nucleotide changes**. Ribosomes move 3 nucleotides at a time, 1 codon at a time. The code is nonoverlapping and commaless. If a single nucleotide is removed from a series of codons, every codon after the deletion suffers a frame shift. Completely different codons give completely different amino acids and resulting proteins. This can produce amino acids chains that aren't only different but of variable length—a premature stop incurs shorter proteins, whereas loss of a stop codon makes it much longer. This is in addition to completely different amino acid sequences that make the new protein useless.

Splice site mutation can be caused by a change or deletion. The "start," "stop," and "here's an intron" all have a code. If the "here's an intron" signal is removed, the thing that should be spliced out doesn't get spliced out; it just keeps going until it gets to a stop or splice signal. The result is variable. You might lose an exon (links exon 1 to exon 3, having never seen the start of exon 2), or you might code useless spacer DNA. Like a frameshift mutation, the result is unpredictable but generally not good. The variations are many, and memorizing them all is silly. The variation is end exon, start exon, or early onset switch in the middle of exons or introns. Predicting is not possible. Just know it's bad.